REMARKS

Upon entry of the foregoing amendments, claims 1, 7-13, 15-27 and 36-41 will be pending in the application. Composition claim 1 and process of use claims 26 and 27 are the only pending independent claims. The Examiner withdrew dependent delivery device claim 24, process of preparation claim 25, and process of use claims 26 and 27 from consideration, since these were the claims that were not provisionally elected, with traverse. Non-elected claims 24-27 have not been canceled, process of use claims 26 and 27 have been amended, and new dependent process of use claims 36-41 have been added in anticipation that they will be rejoined upon the indication of an allowable claim directed to the composition.

Explanation of and Support for the Amendments of the Claims

Claim 1 has been amended, without prejudice, to refer to "a nasal or ocular delivery composition," rather than "a composition ... for nasal or ocular delivery," and the therapeutic agent has been amended, without prejudice, to "a systemically acting therapeutic agent," rather than "a therapeutic agent intended for systemic action" to more particularly and directly claim these properties of the composition. To provide greater clarity for "systemic circulation," claim 1 also has been amended to clarify that the systemic circulation is "an animal's systemic circulation" which would be readily apparent to anyone of ordinary skill in the art in view of the disclosure of systemic circulation, at least at page 14, lines 12-13, of the Substitute Specification, filed with the U.S. National Stage filing on August 21, 2006, in view of the disclosure of the administration of the composition for transport of a therapeutic agent across the mucosal surface to animals, at least at page 16, lines 9-13, 18-21 and 26-29 in the Substitute Specification.

Claim 1, and withdrawn independent claims 26 and 27, as well as dependent claims 18 and 19, have been amended, without prejudice, to recite that the plasticizer is triethyl citrate, which was originally set forth in claim 6, which has now been cancelled, without prejudice, as redundant.

Claim 1 also has been amended, without prejudice, to recite that the composition is in a form for delivery in the form of a spray or drops, which also relates to a property of the composition. Similarly, independent process of use claims 26 and 27 have been amended,

without prejudice, to recite administration or delivery of the composition in the form of a spray or drops. This is supported in the Substitute Specification, filed with the U.S. National Stage filing on August 21, 2006, at least at page 14, lines 22-23.

Withdrawn process of preparation claim 25 has been amended to recite the inclusion of triethyl citrate, in view of the inclusion of this component in claim 1, from which claim 25 depends. Support for this amendment is found at least in the first paragraph at page 16 of the Substitute Specification.

New process of use claims 36-38, depending directly or indirectly from claim 26, and substantially identical process of use claims 39-41, depending directly or indirectly from claim 27, have been added to cover more specifically and separately the ocular and nasal administration or delivery of the composition as stated alternatively in claims 26 and 27, and to cover the presently preferred nasal delivery to a human. The administration or delivery to a human is supported the Substitute Specification at least at page 16, lines 9-13, 18-21 and 26-29.

A couple of minor punctuation amendments have been made to claims 26 and 27.

Since all of the foregoing amendments are supported by the application as filed and no new matter has been added, entry of the foregoing amendments is respectfully requested.

Obviousness Rejection Under 35 U.S.C. § 103(a)

The Examiner considered that the compositions as previously claimed would have been obvious in view of the disclosure of Chenite *et al.* U.S. Patent 6,344,488 ("Chenite") in view of Dunn *et al.* U.S. Patent 5,702,716 ("Dunn") and Illum U.S. Patent 5,629,011 ("Illum"). None of these documents, whether considered alone or combined, and even assuming only for the sake of argument that it would be reasonable to combine the documents, are particularly relevant to the compositions as now claimed and do not render the claimed invention obvious. Applicants accordingly traverse the rejection on the following grounds.

In the Office Action, the Examiner acknowledged that the subject matter claimed is not obvious in view of the disclosure Chenite in combination with Dunn. Therefore, as far as

addressing the Examiner's rejection is concerned, the question to be answered is whether or not Illum provides the teaching missing from the other two documents.

However, it is first worth reviewing what is currently claimed and then considering the Examiner's conclusions about the disclosure of each of these documents and whether their combination is realistic and appropriate.

With reference to Dr. Watts' Declaration, paragraph 4 summarizes the presently claimed invention. The present invention is directed to a composition for delivery of systemically-acting therapeutic agents to a mucosal surface, where such compositions comprise chitosan or the claimed derivatives, salts and salts of derivatives of chitosan, along with a polyol-phosphate or sugar-phosphate salt and a plasticizer, for effective delivery of the therapeutic agent nasally or ocularly. One of the unique features of the compositions of the invention is that they are in the form of an aqueous solution or suspension prior to use, but form a gel at physiological temperatures, such that a gel is formed shortly after application to the mucosal surface of the nose or eye. Thus, a way to assess the suitability of certain compositions for delivery of the systemically-acting therapeutic agent is to determine which plasticizer results in a gel in physiological temperature conditions, for humans a temperature of about 35°C to about 37°C at the mucosal surface of the nasal cavity or eye, *i.e.* the site to which the therapeutic agent is delivered. By forming a gel at the mucosal surface, the therapeutic agent passes more effectively into the systemic circulation of the animal to which the systemically-acting therapeutic agent is administered or delivered. This is a surprising and unexpected feature of the combination of the chitosan polyol-phosphate or sugar-phosphate salt and the triethyl citrate.

The use of triethyl citrate as the plasticizer component of the composition, resulting in a uniquely rapid increase in viscosity and gelation at the physiological temperature was unpredictable and very surprising (Dr. Watts' Declaration, paragraph 9, supported by the data of Annex A to Dr. Watts' Declaration), which provides the composition with its beneficial delivery aspects.

At the bottom of page 4 and page 5 of the Office Action, the Examiner commented on the disclosure of Chenite. There, the Examiner has alleged that Chenite teaches that nasal or ophthalmic drug or peptide delivery can be effected by chitosan-based drug delivery systems.

The sections of text in columns 1 and 2 of Chenite to which the Examiner has referred relate to the prior art and not specifically to the teaching of Chenite. The text at column 5, lines 1 and 2 to which the Examiner has referred states that the gel of Chenite can be used as a whole, or as a component of, ophthalmological implants or drug delivery systems. However, it is clear from the teaching of Chenite as a whole that this document is concerned mainly with compositions used as implants, rather than as sprays or drops.

Likewise, Dunn is concerned with compositions used in implants such as those that provide long term drug release. The possibility of placing an implant in the eye or the nasal cavity is mentioned at column 3, lines 34 to 45. It is clear that these compositions must be delivered in a controlled manner, for example, by a syringe, needle, cannula or catheter. Use of these delivery methods ensures that the implant is delivered to the target site. This is different from the compositions of the invention that are delivered as a spray or in drops. Delivery by spray or drops does not so accurately target the site of application. These delivery methods are not suitable for delivery of implants that will remain in the body for a considerable period of time.

Illum describes compositions in the form of an aqueous solution or suspension for nasal delivery of a therapeutic agent. However, there is nothing in Illum or in either of the other cited references that would have motivated a skilled person to combine the teaching of these documents. Chenite and Dunn are quite clearly directed to compositions that are intended to stay in the body for a considerable period of time, such as implants. If these compositions comprise a drug compound, that drug compound is released into the body over a period of days or longer. This is a completely different type of drug release and therapeutic application to that which is described in Illum. The skilled person seeking to produce a composition that could be delivered using a spray or drops would not have considered the teaching of Chenite or Dunn, let alone the combination of both documents with Illum.

Even assuming only for the sake of argument that the skilled person would have considered all three documents in combination, he still would not have arrived at the present invention. It is an essential feature of the compositions as now claimed that they comprise triethyl citrate as a plasticizer. As noted by the Examiner, Dunn suggests that the compositions it describes can comprise a rate modifying agent, which may be triethyl citrate. The properties

of the rate modifying agent are discussed in column 8 of Dunn. One purpose of the rate modifying agent is to ensure that the implant is soft, resilient and flexible in the body. These are features that are required of a composition that will remain in the body for a long period of time, a matter of days, months or even years. They are not features that are important in compositions delivered in the way that the compositions of the present invention are delivered. Another important feature of the rate modifying agent used in Dunn is that it provides for sustained release of the drug compound over a period of days, or even longer. For example, a period of time of about 14 days is mentioned at column 7, lines 39 to 41 of Dunn. Testing for a period of 20 days was conducted in Example 1 of Dunn.

The composition of the invention is not designed to and will not stay in the body for this length of time. Rather than making the use of triethyl citrate obvious, the teaching of Dunn would have actively discouraged the skilled person from using triethyl citrate in compositions of the type claimed in the present application. They would have understood the teaching of Dunn as showing that triethyl citrate significantly inhibits drug release to the extent that inadequate drug release would occur in the time period in which a composition according to the invention remains in the nasal cavity. Thus, it would not have been obvious to use triethyl citrate in the compositions of the invention. Additionally, Applicants have found that the use of triethyl citrate in the compositions of the invention provides surprising and unexpected advantages.

One of the unique features of the compositions of the invention is that they are in the form of an aqueous solution or suspension prior to use but form a gel at physiological temperatures such that a gel is formed shortly after application to the mucosal surface of the nose or eye. As supported by Dr. Watts' Declaration and its Annex A, this is a surprising, unexpected and unpredictable feature of the combination of the chitosan polyol-phosphate or sugar-phosphate salt and the triethyl citrate.

In the paragraph bridging pages 2 and 3 of the Substitute Specification, the difficulties associated with providing a composition having these properties is discussed. It has not previously been possible to provide a composition that behaves in this manner.

As explained in detail in Dr. Watts' Declaration at paragraphs 4-9 and Annex A, Applicants unpredictably and therefore very surprisingly, found unique properties when triethyl

citrate is used as a plasticizer in a composition comprising chitosan, a salt thereof or a derivative thereof as defined in claim 1 and a polyol-phosphate or sugar-phosphate salt in an aqueous solution or suspension that can be administered or delivered to an animal, including humans, in the form of a spray or drops as also set forth in claim 1. The data of Annex A show that the effect of uses of various plasticizers, and particularly triethyl citrate, is not at all predictable. When triethyl citrate is used as a plasticizer in the composition, the viscosity of the composition increases rapidly at physiological temperatures to form a gel; this should enable a systemically-acting therapeutic agent to be more effectively delivered to the systemic circulation since the period of time which the composition remains in contact with the mucosal surface is increased. In contrast, other known plasticizers did not result in a composition that had such a rapid increase in viscosity to quickly form a gel.

No less than 10 potential plasticizer materials were tested and triethyl citrate was surprisingly found to be the only material that provided a composition that would form a gel in a manner ideal for use in nasal or ocular drug delivery.

Three of the materials tested did not have a suitable aqueous solubility. Three of the materials did not provide a composition that formed a gel at the temperature found in the nasal cavity or in the eye. The PEG materials prohibited gel formation at high concentrations and provided slow incomplete gel formation at lower concentrations. See Dr. Watts' Declaration, paragraph 7 and Annex A.

The only materials that did gel were triacetin and triethyl citrate. Triacetin containing compositions gelled relatively slowly at 35°C and even more slowly at 37°C. Clearly, rapid gelling at the temperature found in the eye or in the nose is advantageous for ocular and nasal drug delivery compositions as this reduces loss of the composition caused by the composition dripping out of the eye or nose; the drug remains in contact with the mucosa for a longer period, thus increasing the effectiveness of absorption. Dr. Watts' Declaration, paragraph 8.

Only the use of triethyl citrate provided a composition with gelling properties advantageous for use in a nasal or ocular drug delivery composition. This is surprising and unexpected.

None of the cited prior art documents discloses or suggests the use of triethyl citrate to alter and enhance the gelling properties of a composition comprising a chitosan and polyol

phosphate or sugar-phosphate salt which is delivered in the form of spray or drops. The invention as now claimed and its advantages were not obvious to the inventors and would not have been obvious to a person of ordinary skill in the art in view of any of these documents alone or in combination. Dr. Watts' Declaration, paragraph 10.

Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Moreover, reconsideration and withdrawal of the restriction requirement and the rejoinder of the provisionally non-elected claims, and an early Notice of Allowance with respect to all pending claims are respectfully requested.

Respectfully submitted,

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Nov. 12, 2010 By: _____
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